**REMARKS**

Claims 1, 2, 4-10 and 12-15 are pending in the instant application. Claims 1, 2, 4-10 and 12-15 have been rejected. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Restriction/Election**

The Restriction Requirement requiring restriction to a single region, the coding region, within SEQ ID NO: 3 has been deemed proper and made Final. Applicants acknowledge the Examiner's action regarding the pending application and the claims and have amended the claims accordingly.

**II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph**

Claim 15 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is

enabling for compounds 8 to 50 nucleobases in length that target and inhibit expression of fibroblast growth factor receptor 2 *in vitro* but suggests that the specification as filed is not enabling for *in vivo* uses of the claimed antisense compounds. The Examiner cites several articles on the technology of antisense to support the position regarding extrapolation to *in vivo* and pharmaceutical uses. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to two articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including

antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The Examiner has also pointed to an article that discusses the role of fibroblast growth factors and their receptors in signaling. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects for these molecules is unpredictable.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 to recite that the method is an *in vitro* method. Therefore, withdrawal of the rejection is requested.

**III. Rejection of Claims Under 35 U.S.C. 102**

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Wilson et al. (GenEMBL Accession No. 132954) has

been maintained for reasons of record. The Examiner suggests that this citation discloses a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity.

Applicants respectfully point out that in the Office Action response filed April 2, 2003, the claims were amended to recite antisense compounds targeted not to the coding region but to specific nucleobase regions within the coding region. These nucleobase regions did not include the region referred to in the reference cited (*i.e.*, nucleobases 1242 through 1271). Therefore, contrary to the Examiner's suggestion, this reference cannot anticipate the claims as amended in April 2003 as it fails to teach the limitations of those claims (see MPEP 2131). Further, the reference also fails to teach the limitations of the currently amended claims which specified compounds targeted to nucleobases 1317 through 2720 of the coding region of SEQ ID NO: 3. Withdrawal of this rejection is therefore respectfully requested.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Wilson et al. (GenEMBL Accession No. 187104) has

been maintained for reasons of record. The Examiner suggests that this citation discloses a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity.

Again, Applicants respectfully point out that in the Office Action response filed April 2, 2003, the claims were amended to recite antisense compounds targeted not to the coding region but to specific nucleobase regions within the coding region. These nucleobase regions did not include the region referred to in the reference cited (*i.e.*, nucleobases 1242 through 1271). Therefore, contrary to the Examiner's suggestion, this reference cannot anticipate the claims as amended in April 2003 as it fails to teach the limitations of those claims (see MPEP 2131). Further, the reference also fails to teach the limitations of the currently amended claims which specified compounds targeted to nucleobases 1317 through 2720 of the coding region of SEQ ID NO: 3. Withdrawal of this rejection is therefore respectfully requested.

The rejection of claim under 35 U.S.C. 102(b) as being anticipated by Chenchik et al. (GenEMBL Accession No. AR090312) has

been maintained for reasons of record. The Examiner suggests that this citation discloses a 25 base pair keratinocyte growth factor receptor downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity.

As discussed above, Applicants respectfully point out that in the Office Action response filed April 2, 2003, the claims were amended to recite antisense compounds targeted not to the coding region but to specific nucleobase regions within the coding region. These nucleobase regions did not include the region referred to in the reference cited (*i.e.*, nucleobases 1179 through 1203). Therefore, contrary to the Examiner's suggestion, this reference cannot anticipate the claims as amended in April 2003 as it fails to teach the limitations of those claims (see MPEP 2131). Further, the reference also fails to teach the limitations of the currently amended claims which specified compounds targeted to nucleobases 1317 through 2720 of the coding region of SEQ ID NO: 3. Withdrawal of this rejection is therefore respectfully requested.

**IV. Rejection of Claims Under 35 U.S.C. 103(a)**

Claims 1, 2, 4-10 and 12-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (1999), and further in view of Baracchini et al. (US Patent 5,801,154) and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to make antisense oligonucleotides as claimed because the art teaches the role of this molecule in cell growth regulation (Yamada et al.). The Examiner suggests that one of skill would have had a reasonable expectation of success based on the teachings of Baracchini et al. in teaching antisense to a coding region of a gene. The Examiner suggests motivation to modify antisense is provided by the teachings of Fritz et al. and Baracchini et al. Applicants respectfully traverse this rejection.

At the outset, Applicants amended the claims in the Office Action response of April 2003, as discussed *supra*, to list specific nucleobase regions within the coding region of human fibroblast growth factor receptor 2 of SEQ ID NO: 3 that are to be targeted by antisense compounds, regions that did not include the translation start site. These regions are taught in the specification as filed at pages 85-88. The claims have now been

further amended in response to a Restriction Requirement to recite one specific nucleobase region within the coding region of SEQ ID NO: 3.

Yamada et al. (1999) disclose use of a phosphorothioate antisense oligonucleotide of unspecified length that was complementary to the translation start site of fibroblast growth factor receptor 2 and its use in cells to investigate the role of this molecule in signaling in human glioblastoma cells. Nowhere does this reference teach or suggest any antisense sequences as now claimed which are targeted to a specific region of fibroblast growth factor receptor 2, a region that does not include the translation start site. Therefore, this primary reference fails to teach or suggest use of antisense compounds targeted to the region now claimed.

The secondary references cited fail to overcome the deficiencies in teaching of the primary reference.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions of the human fibroblast growth factor receptor 2

(SEQ ID NO: 3) and the successful inhibition of expression using antisense.

Fritz et al. (1997) disclose cationic polystyrene nanoparticles as carrier systems for antisense compounds in general. This paper, however, does not teach or suggest use of antisense compounds of any type to target the human fibroblast growth factor receptor 2 (SEQ ID NO: 3), or any region within the sequence of this nucleic acid molecule, and the successful inhibition of expression using antisense.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as now amended, which specify a specific region within the sequence of fibroblast growth factor receptor 2 (SEQ ID NO: 3), are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or

suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It is only with the specification in hand that one of skill would understand that a specific region of fibroblast growth factor receptor 2 as claimed could be targeted successfully with antisense compounds. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

**V. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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